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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	Byoung Se Kwon
Serial No.:	08/012,269
Filed:	2/01/93
For:	NEW RECEPTOR, MONOCLONAL ANTIBODY, LIGAND PROTEIN AND METHODS FOR USE
Examiner:	J. Ellis
Art Unit:	1813

APPEAL BRIEF

Commissioner of Patents and Trademarks
Washington, D.C. 20231

This application is before the Honorable Board of Appeals on appeal from the final rejection by the Examiner dated April 1, 1994, wherein claims 1-4 were finally rejected.

The fee of $135.00 is attached.

(1) STATUS OF CLAIMS

Claims 1-4 and 6-21 are pending in the application. Claims 6-21 have been withdrawn from consideration pending the filing of a divisional or continuation application and claim 5 was cancelled by the applicant. Claims 1-4 were rejected under 35 U.S.C §101. Claim 4 was rejected under 35 U.S.C. §112, first and second paragraphs. Claims 1-4 were rejected under 35 U.S.C §103.

(2) STATUS OF AMENDMENTS

The amendments made in the response dated December 17, 1993 was entered. The amendment to the specification made after the final rejection dated July 1, 1994 was entered.

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(3) SUMMARY OF THE INVENTION

The present invention is a novel cDNA sequence, 4-1BB, that encodes a receptor protein. The applicant used a differential screening process to isolate 16 subset clones. Fourteen of the initial isolates were sequenced and found to be five distinct species. Of these five, three were discovered to be known proteins and the remaining two were novel sequences. 4-1BB was one of the novel sequences.

The protein encoded by 4-1BB was discovered to be a receptor. Cells expressing 4-1BB stimulate B-cell proliferation, therefore, recombinant 4-1BB is useful as an agent to suppress the immune response during organ transplantation by binding on the receptors to 4-1BB. A monoclonal antibody 53A2 against 4-1BB can be used to enhance T-cell proliferation.

References Relied Upon or Made of Record by the Examiner

a) Kwon *et al.*, Proc. Natl. Acad. Sci. 84:2896 (1987); and

b) Maniatis *et al.*, Cold Spring Harbor Laboratory, pp. 310-352 (1982)

(4) ISSUES

I. The first issue is whether the utility recited in the specification is sufficient to satisfy the requirements of 35 U.S.C. §101.

II. The second issue is whether the specification provides an adequate written description and an enabling disclosure for claim 4 under 35 U.S.C. §112, first paragraph and whether claim 4 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention under 35 U.S.C. §112, second paragraph.

III. The third issue is whether claims 1-4 are obvious in view of Kwon *et al.* and Maniatis *et al.*. under 35 U.S.C. §103

(5) GROUPING OF CLAIMS

The rejected claims do not stand or fall together.

Claims 1-3 are argued as a group and stand or fall together.

Claim 4 is argued separately.

(6) ARGUMENT

With Respect to Issue I

The Examiner rejected claims 1-4 under 35 U.S.C. §101 arguing that the specification did not recite a patentable utility.

Referring to the rejection, the Examiner states that:

"First, the descriptive characteristics disclosed in the specification are the initial experimental steps performed in order to ascertain what is the actual biological role and/or use of 4-1BB. These characteristics do not disclose (i) the biological activity for 4-1BB, or (ii) how to use 4-1BB. Second, the expression of 4-1BB in different cell types does not provide a patentable utility for the protein because this characteristic does not disclose its function or how to use the protein. The cross-linking of 4-1BB with a monoclonal antibody is not evidence of the actual activity of 4-1BB. the specification teaches that these data merely suggest that 4-1BB has the potential to function as an accessory signaling molecule during T cell activation and proliferation. See p. 56, lines 22-25. The specification discloses that the experiments involving the paraformaldehyde-fixed sf21 cells expressing recombinant 4-1BB which synergized with f(ab'), anti-mu to induce splenic B-cell proliferation merely suggest that 4-1BB may act as a regulator for B-cell growth. See p. 678, lines 24-28. Accordingly, the specification is merely speculating as to possible roles of 4-1BB, but fails to disclose how one skilled in the art can use the invention."

The Examiner's statements are incorrect. The specification provides detailed analysis of the expression and function of the 4-1BB gene and protein. 4-1BB is an inducible receptor-like protein expressed in both cytolytic and helper t-cells, PMA-treated spleen cells, heart cells, kidney cells and the brain. (see Page 25, lines 10-13; Page 39, line 17 - Page page 43, line 9) Crosslinking of 4-1BB on anti-CD3-stimulated T cells with the monoclonal antibody, 53A2, resulted in a dramatic enhancement of T cell proliferation. (Page 43, lines 12-26) This is not speculative, this activity was demonstrated conclusively by the disclosed data. What is speculative is whether 4-1BB's **primary** purpose in mice is to regulate T cell proliferation, but this does not change the fact that 4-1BB effects on T cell proliferation. This may just be an extremely useful side effect to a receptor protein that is primarily involved in some completely different regulatory function. However, this is irrelevant for the purposes of patentability. The Examiner is overly concerned with determining the exact mode of action of the 4-1BB in vivo. It is not necessary that the applicant know all of the details or even any of the details of the primary role of 4-1BB in vivo. The bottom line is that 4-1BB (by being used to create the monoclonal antibody) has been shown to have a utility in enhancing T cell proliferation. This effect of the treatment described is important to any problem in an organism that results in a low T-cell count (eg. AIDS) or in culturing of cells (secondary utility).

Furthermore, 4-1BB can be used to either induce or suppress (by ligand blocking) B-cell proliferation. (See Page 5, lines 10-21) Like any good scientist, the applicant realizes that there is a lot more to learn about 4-1BB, however, this does not mean that there is not a great deal known already. Frankly, there is no invention that could not use further analysis. The entire concept of invention is based upon further discovery and improvement. The specification includes many references to potential new areas of study and further research possibilities but this does not mean that nothing is known about 4-1BB or its function. The effects of 4-1BB have been discovered, specifically, T-cell proliferation and activation and B-cell proliferation and suppression through ligand binding. Doctors know that ibuprofin cures a headache but they know relatively little about how it cures the headache. The applicant has clearly demonstrated how 4-1BB, the monoclonal antibody can be used in a utilitarian way.

The limitations of 35 U.S.C. §101 as interpreted in Brenner v Manson 383 U.S. 519, 148 U.S.P.Q. 689 (1966) requires that the utility must be a practical utility, however, this practical utility does not have to rise to the level of a commercial utility.

Brenner v Manson related to a process for making a steroid with no known function. The applicant had demonstrated that the 4-1BB cDNA is the starting point for numerous useful treatments.

The present specifications satisfies the requirement of 35 U.S.C. §101 by teaching the uses for the 4-1BB cDNA, protein and monoclonal antibody. Therefore, the reversal of this rejection is requested.

With Respect to Issue II

The Examiner has rejected claim 4 under 35 U.S.C. §112, first and second paragraphs arguing that the specification does not provide an adequate written description or an enabling disclosure and that the word "similar" is indefinite.

As a preliminary note, the Examiner continually cites In re Langer, 503 F.2d 1380, 183 U.S.P.Q. 288 (CCPA 1974) and In re Payne, 203 U.S.P.Q. 245 and states that the arguments are merely arguments of counsel and can not take the place of objective evidence. These comments are not understood. Counsel is certainly capable of posing legal arguments and referring to the specification without the need for declarations. All of the information relied upon by the applicant's attorney is found in the specification, the applicant's attorney has not referred to any information or data not included in the specification with regard to this issue. Therefore, the Examiner's citing of these cases and surrounding comments are not understood.

The Examiner objects to the use of the phrase "fragments and derivatives" as used in claim 4 arguing that the specification does not teach what "fragments" or "derivatives" are intended. This is not true. The applicant discloses that the probes must be capable of being used to isolate similar sequences. This is a functional limitation, not a mere recitation of an intended use. The term "similar" is not vague or indefinite because, a DNA probe can not by used to determine anything other than homology. DNA probes are not used in activity assays for lymphokines. Activity assays measure the level of activity of a desired enzyme or can be used to determine whether a particular protein is present or absent. DNA probes are not enzymes and there do not exhibit characteristic activities. The intercrine ß superfamily is referred to in the application and the conserved sequence fragments are identified in the application on Page 38, line 28 - Page 39, line 16, (see figure 17) and would make the most likely

candidates for probes. This is well known and inherent from the information provided to anyone skilled in the art. Furthermore, many modifications can be made to the cDNA sequence without affecting the encoded amino acid in any way. Therefore, many derivatives are easily contemplated without any affect on the coded protein. These substitutions can be discovered merely by looking on a table listing the codons for each amino acid in any biochemistry book.

For reasons set forth above, the rejection of claim 4 under 35 U.S.C. § 112, first and second paragraph, is believed to be in error. Therefore, the reversal of the Examiner's rejection is requested.

With Respect to Issue III

The Examiner rejected claims 1-4 under 35 U.S.C. §103 arguing that they are obvious in view of Kwon *et al.* and Maniatis *et al.*.

Kwon *et al.* only identified several cDNA clones which were partial fragments of the genes claimed herein. Nothing in Kwon *et al.* taught which subset clones corresponded to the full length clone disclosed herein. Although that paper disclosed part of the method used to make this invention, it did not teach the complete structure of the cDNA sequence of the present invention. Although, it may be argued that the results of the prior paper might have made it obvious to try to determine the genes from which the fragments might have come, there was no indication in that work that the genes would be found, nor that those genes in their complete form would have the properties of 4-1BB as disclosed in the specification. In fact many of the subset clones were fragments of the previously known gene sequences. Although Maniatis et al does teach relevant techniques used in molecular biology, nothing in that reference would give a researcher skilled in the art reasonable expectation of success that those subset clones could be used to isolate the 4-1BB cDNA sequence having the properties disclosed in the specification. It was unknown whether these subset cDNA clones corresponded to novel proteins until the work disclosed in the specification.

Kwon et al does not put the actual subset clones into the hands of the public. Only the present inventor had the actual clone. Merely stating that a subset clone exists is insufficient to enable one skilled in the art to obtain it. See Fiers v Revel *et al.*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601, CAFC (1993). This is the reason for the deposit

rules with regard to biotechnology inventions. Synthesizing the sequence was not possible because no sequence was given. Following the same procedure would not necessarily produce the same subset clones and without access to the original subset clones it would be impossible to know whether the same clones had been made or not.

The Examiner has failed to recognize the importance of the teachings of the present invention that specifically identify the expression of the cDNA sequence. The sequence data disclosed in the present application was also important in determining which of the 14 initial cDNA isolates corresponding to the five species identified. Therefore, the two novel species L2G25B and 4-1BB were not positively identified until the sequence data was performed. While sequencing may have been obvious to try, the results of the sequence data were not obvious.

Furthermore, the Examiner relies on methods taught by Maniatis *et al.* The Examiner seems to be stating that for a product claim to patentable, the methods used to obtain the product must be non-obvious. There is no requirement in patent law that a product be produced by non-obvious methods but only that the product itself be non-obvious. (See *In re Thorpe*, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985)) The Federal Circuit recently upheld this principle of patent law in *In re Bell* which held that the gene for human insulin like growth factors I and II (IGF) were not rendered obvious by the previously disclosed amino acid sequences. (1993 U.S. App. LEXIS 8603, decided 4/20/93, (Fed. Cir. 1993), See also *Amgen v. Chugai Pharmeceuticals*, (CAFC 1991) 927 F.2d 1200, at 1206, 18 U.S.P.Q.2d 1016)

If an inventor knows that a particular gene exists (i.e. by previous isolation of a protein, etc.) but nothing more about its location, length or sequence such that the inventor is unable to distinguish it from other materials and to describe how to obtain it, he/she has not sufficiently conceived the invention. In *Amgen v. Chugai Pharmaceuticals*, the Court of Appeals for the Federal Circuit stated:

> "Conception does not occur unless one has a mental picture of the structure of the chemical, or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define [a DNA sequence] by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." (CAFC 1991) 927 F.2d 1200, at 1206, 18

U.S.P.Q.2d 1016, followed *Fiers v. Revel*, (CAFC 1993) 984 F.2d 1164, 25 U.S.P.Q.2d 1601.

There has been no similar products to the cDNA claimed by the applicant. The rejection of claims 1-4 is clearly in error. The products recited in claims 1-4 were not suggested by or obvious in view of the teachings of Kwon *et al.* considered with the teachings of Maniatis *et al.*.

Based upon the foregoing arguments, the applicants and the applicants' attorney believe that claims 1-4 are allowable under 35 U.S.C. §103 and request that the Board reverse the Examiner's rejection.

Conclusion

Based upon the arguments made herein, the applicant requests that the Examiner's rejection of claims 1-4 be reversed and that claims 1-4 be allowed to go to issue.

Respectfully Submitted:
Byoung Se Kwon,

By: _____
Christopher A. Michaels
Reg. No. 34,390
Attorney for Applicant

BARNARD, BROWN & MICHAELS
306 E. State St., Suite 220
Ithaca, NY 14850
607-273-1711
607-273-2609 (fax)

CERTIFICATE OF MAILING

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Judy H. Barron
Judy Barron

APPENDIX

BOARD OF PATENT APPEALS AND INTERFERENCES

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The Claims On Appeal

1. A cDNA sequence which encodes for receptor protein 4-1BB.

2. The cDNA sequence of claim 1 having a nucleotide sequence as shown in Figures 2a and 2b.

3. The cDNA sequence of claim 1, identified as p4-1BB deposited at the American Type Culture Collection at 12301 Parklawn Drive, Rockville, Maryland 20852 under ATCC No.: 67852.

4. The cDNA of claim 2 and fragments and derivatives thereof, wherein said fragments and derivatives can be used as a probe to isolate DNA sequences encoding for proteins similar to the receptor protein encoded by said cDNA.